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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,519	07/06/2001	Keith D. Allen	R-615	3963

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EXAMINER	
PARAS JR, PETER	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/900,519	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicant's amendment received on 10/20/03 has been entered. Claims 1-24 have been cancelled. New claims 25-33 have been added. Claims 25-33 are pending and are under current consideration.

Specification

The amendment to the brief description of the drawings has been entered.

Sequence Compliance

The instant application is now in sequence compliance.

Upon further consideration the following new grounds of rejection under 35 U.S.C. 101 are necessary:

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 25-33 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claims are directed to a transgenic mouse whose genome comprises a disruption in the endogenous adrenomedullin receptor gene comprising the nucleotide sequence set forth in SEQ ID NO: 1, wherein the mouse exhibits decreased activity or

increased anxiety as characterized by open field testing. The claims are further directed to a method of producing the same transgenic mouse.

The instant specification has contemplated that the nucleotide sequence set forth in SEQ ID NO: 1 encodes an adrenomedullin receptor. The instant specification has further contemplated that disruption of the nucleotide sequence set forth in SEQ ID NO: 1 in a mouse will produce a phenotype related to an adrenomedullin receptor. The instant specification has purported that such mice may be used to identify agents that modulate or ameliorate a phenotype associated with a disruption in SEQ ID NO: 1.

The instant specification has disclosed a transgenic mouse whose genome comprises a disruption in SEQ ID NO: 1, wherein the mouse exhibits decreased activity characterized by reduced distance traveled in an open field or by reduced average velocity in an open field or increased anxiety characterized by reduced average velocity in an open field. The claims embrace such a mouse and a method of making the mouse. The instant specification has discussed that phenotypes exhibited by such a transgenic mouse could correlate to a disease or disorder. However, the evidence of record does not provide a correlation between decreased activity characterized by reduced distance traveled in an open field or by reduced average velocity in an open field or increased anxiety characterized by reduced average velocity in an open field and any disease or disorder. Moreover, while the specification has purported that the nucleotide sequence set forth in SEQ ID NO: 1 encodes an adrenomedullin receptor, the evidence of record has failed to provide a correlation between any adrenomedullin receptor related disease/disorder and decreased activity characterized by reduced

distance traveled in an open field or by reduced average velocity in an open field or increased anxiety characterized by reduced average velocity in an open field. The specification has provided general assertions that the claimed transgenic mice may be used to identify agents that affect a phenotype related to the mice.

As such, the asserted utility, for the transgenic mouse embraced by the claims, of screening agents that may affect a phenotype of said mouse as provided by the instant specification and encompassed by the claims, does not appear to be specific and substantial. The asserted utility does not appear specific and substantial to the skilled artisan since the evidence of record has not provided any suggestion of a correlation between any adrenomedullin receptor, decreased activity characterized by reduced distance traveled in an open field or by reduced average velocity in an open field or increased anxiety characterized by reduced average velocity in an open field, and any disease or disorder. Since the evidence of record has not provided a correlation between decreased activity characterized by reduced distance traveled in an open field or by reduced average velocity in an open field or increased anxiety characterized by reduced average velocity in an open field, the utility of identifying agents that affect decreased activity characterized by reduced distance traveled in an open field or by reduced average velocity in an open field or increased anxiety characterized by reduced average velocity in an open field is not apparent. The evidence of record has not provided any other utilities for the transgenic mouse embraced by the claims that are specific, substantial, and credible.

The asserted utility of the transgenic mouse embraced by the claims is based on the expectation that disrupting the nucleotide sequence set forth in SEQ ID NO: 1 would result in a detectable phenotype in the mouse. The phenotype observed in the transgenic mice embraced by the claims is decreased activity characterized by reduced distance traveled in an open field or by reduced average velocity in an open field or increased anxiety characterized by reduced average velocity in an open field. While the phenotypes exhibited by the claimed transgenic mouse are contemplated to be associated with a disease, the association of decreased activity characterized by reduced distance traveled in an open field or by reduced average velocity in an open field or increased anxiety characterized by reduced average velocity in an open field with any disease has yet to be elucidated. In fact the art suggests that results obtained from behavioral studies, such as the open field test, are greatly influenced by the genetic background of the tested mouse. Crabbe et al (Science, 1999, Vol. 284, pages 1670-1672) observed that laboratory environment and site, test conditions, and genetic strain of a mouse influence the results of behavioral studies. See pages 1670-1671. With regard to the open field test, Crabbe reports that A/J mice were relatively inactive, while C57BL/6 mice were very active. Crabbe further reports that on average mice tested in Edmonton were more active than those tested in Albany or Portland. See page 1671, column 1, the first full paragraph. Crabbe discusses that such inconsistencies in test results can be responsible for observed behavioral phenotypes. Given the inconsistencies in behavioral test results, Crabbe concludes by cautioning that specific behavioral effects observed in mutant (knockout) mice should be not be

uncritically attributed to genetic manipulations prior to repeating testing in different laboratories using different strains of mice, if possible. See page 1672, column 1, paragraphs 2-3. With regard to increased anxiety as related to open field testing, Belzung et al (Behavioural Brain Research, 2001, 125: 141-149) suggest limited usefulness of models of anxiety based on a single gene deletion, which alone can hardly account for a complex condition such as anxiety. See page 147, in the last paragraph. Belzung et al also discuss the differences in anxiety levels among different strains of inbred mice and provide evidence correlating the different genetic backgrounds of the mice and differences in levels of anxiety as measured by the open-field test. See pages 146-147.

Therefore, the reference suggests a need to provide independent evidence of an association of decreased activity characterized by reduced distance traveled in an open field or by reduced average velocity in an open field or increased anxiety characterized by reduced average velocity in an open field with a disease or disorder. However, neither the specification nor any art of record provides evidence of the existence of a correlation between decreased activity characterized by reduced distance traveled in an open field or by reduced average velocity in an open field or increased anxiety characterized by reduced average velocity in an open field and a disease or disorder, leaving the skilled artisan to speculate and investigate the uses of the transgenic mouse embraced by the claims. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the transgenic mouse embraced by the claims. In light of the above, the skilled artisan would not find the

asserted utility of the transgenic mouse embraced by the claims to be specific and substantial.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-33 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition to the above, the following grounds of rejection under 35 U.S.C. 112, 1st paragraph are necessary:

Claims 25-33 encompass transgenic non-human animals that comprising a disruption in an endogenous adrenomedullin receptor gene. The claims can be interpreted to read on transgenic mice having either a heterozygous and homozygous disruption in the adrenomedullin receptor gene. While the instant specification has provided guidance correlating a homozygous disruption in the adrenomedullin receptor gene with a phenotype of decreased activity or increased anxiety, the instant specification has not provided guidance correlating a phenotype with a heterozygous

disruption of the adrenomedullin receptor gene. The state of the art at the time of filing was such that one of skill could not predict the phenotype of a knockout mouse (See Moreadith et al., 1997, J. Mol. Med., Vol. 75, pages 208-216). In particular, Moreadith et al. discuss that gene targeting at a particular loci is unpredictable with respect to the resulting phenotype since often the generation of knockout mice, in many instances, changes the prevailing notions regarding the functions of the encoded proteins. Moreadith et al. go on to report that gene targeting at the endothelin loci led to the creation of mice with Hirschsprung's disease instead of the anticipated phenotype (abnormal control of blood pressure). See page 208, column 2, 2nd paragraph. Moens et al. (Development, Vol. 119, pages 485-499, 1993) disclose that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null (see abstract). The specification has asserted that the nucleotide sequence set forth in SEQ ID NO: 1 encodes an adrenomedullin receptor. However, given the state of the art it would be difficult to predict any phenotype resulting from disruption of the sequence of SEQ ID NO: 1. The specification discloses that the phenotypes exhibited by transgenic knockout mice comprising a homozygous disruption in the nucleotide sequence set forth in SEQ ID NO: 1 are as follows: decreased activity characterized by reduced distance traveled in an open field or by reduced average velocity in an open field or increased anxiety characterized by reduced average velocity in an open field. See pages 51-52 of the specification. Given the lack of guidance provided by the instant specification, the skilled artisan would know how to use a transgenic knockout

non-human animal that lacks a phenotype, particularly because the instant specification has not provided uses for such; the transgenic mice exhibiting the recited above phenotypes may be used for drug testing according to the instant specification. The specification overcomes the unpredictability in obtaining a phenotype (as discussed above) by correlating a homozygous disruption of the nucleotide sequence set forth in SEQ ID NO: 1 in the genome of a transgenic mouse; however, the claims are not commensurate in scope with the phenotype disclosed in the specification because the claims recite language that reads on transgenic mice that are homozygous or heterozygous for the disruption. As previously discussed only the transgenic mice whose genomes comprise a homozygous disruption of the nucleotide sequence set forth in SEQ ID NO: 1 exhibit the above discussed phenotypes. Given the unpredictable nature of a phenotype that results from disruption of a nucleotide sequence and the lack of guidance provided by the instant specification for use of a transgenic mouse lacking a phenotype, it would have required undue experimentation for the skilled artisan to make and use the invention as claimed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is (571) 272-0732. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at 571-272-0804. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Official Fax Center number is (703) 872-9306.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS
PATENT EXAMINER